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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HOUGHTLING, RICHARD A	
ART UNIT	PAPER NUMBER
4133	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,821	MARX ET AL.	
	Examiner	Art Unit	
	Richard A. Houghtling, Ph.D.	4133	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 18-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 18-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *27 April 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-20 are pending in the application received February 18, 2005; receipt of a Preliminary Amendment filed February 18, 2005 is acknowledged. Applicants' preliminary amendment of claims and abstract are entered into the record, hence claim 17 is cancelled and claim(s) 1-16 and 18-20 are presently pending and examined on their merits, herein.

Foreign Priority

2. Applicants' claim to foreign priority under 35 U.S.C. 119(a)-(d) is acknowledged; a certified copy filed on February 18, 2005 is entered.

Information Disclosure Statements

3. Acknowledgement of receipt of an information disclosure statement filed by applicants on April 27, 2005; disclosure entered into the record and examiner considered references.

Claim Objections

4. Claim 15 is objected to because of the following informalities: brackets should be changed to parentheses and the term "INN:" should be dropped. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 19 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "ciclesonide" in claim 19 is a relative term, which renders the claim indefinite. The phrase "mixing ratio with ciclesonide" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Applicants' claim is to a pharmaceutical composition of an antihistamine and ciclesonide, wherein an epimer of ciclesonide may be utilized (claim 1); because ciclesonide has a chiral carbon, both an R-epimer and an S-epimer could exist as well as a racemate mixture of the two epimers. Since Applicants' specification fails to teach whether the term "ciclesonide" refers to the R-epimer, S-epimer or the racemic mixture of both epimers, one of ordinary skill in the art cannot ascertain how to determine what a mixing ratio with ciclesonide encompasses and thus is indefinite.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-16 and 18-20 are rejected under 35 U.S.C. 103(a) as being obvious over Nagano et al. (US Patent 6,767,901 as cited in applicants' IDS from April 27, 2005) in view of Nishibe et al. (US Patent Application Publication US 2003/0008019 as cited in applicants' IDS from April 27, 2005).

The applied reference (Nagano et al.) has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Instant claims 1-16 and 19 are drawn to a pharmaceutical composition comprising a combination—A) at least one antihistamine and B) ciclesonide (claim 1),

that is further limited to an aqueous solution further comprising one or more water-insoluble and/or water-low soluble substances, wherein the pharmaceutical composition has an osmotic pressure of less than 290 mOsm or less (claim 2); which is further limited by claims 3-6 that define the osmotic pressure of the aqueous solution as ≤150 mOsm, ≤60 mOsm, ≤40 mOsm or ≤20 mOsm; claim 7 adds an osmotic pressure controlling agent; claims 8-10 define the water-insoluble or water low-soluble component as cellulose—microcrystalline, which is in suspension with the water-soluble polymer (claim 11), which is further limited to carboxymethyl cellulose sodium (claim 12); and further comprises a surfactant or wetting agent (claim 13) for application to the mucosa (claim 14). The antihistamine(s) of the pharmaceutical composition of claim 1 is/are defined by a Markush group (claim 15), and restricted to either azelastine or levocabstine (claim 16); and finally, the epimer of ciclesonide is present in any mixing ratio with ciclesonide (claim 19).

Instant claims 18 and 20 are drawn to a method for the treatment of allergic rhinitis or allergic conjunctivitis comprising administration of a therapeutically effective amount of A) at least one antihistamine and B) ciclesonide in a mammal (claim 18), and further when the mammal is a human (claim 20).

Nagano et al. teaches a pharmaceutical composition of ciclesonide for application to the mucosa that possesses greater mucosal retention (i.e., reduced drug

clearance) of ciclesonide at low osmotic pressures (see col. 3, lines 12-21). Nagano et al. further teaches and claims,

> "An aqueous pharmaceutical composition for application to mucosa, comprising one or more water-insoluble and/or water-low soluble substance and ciclesonide, and having an osmotic pressure of 150 mOsm or less," (see claim 1).

Additional claims 2-4 further limit the osmotic pressure of Nagano et al. to less than or equal to: 60 mOsm (claim 2), 30 mOsm (claim 3), or 10 mOsm (claim 4). The Nagano et al. composition further comprises an osmotic pressure-controlling agent (claims 5-9), water insoluble or water-low soluble substance is a cellulose (claim 10), which is further limited to a crystalline cellulose (claim 11); and that the water insoluble or water-low soluble substance is present as solid particles in an aqueous medium (claim 12) which may further comprise a water soluble polymer substance (claim 14) that may be selected as one or more from a Markush group which includes methyl cellulose and carboxymethyl cellulose sodium (claim 15), that is further limited to carboxymethyl cellulose sodium (claim 16), and further limited to crystalline carboxymethyl cellulose sodium (claim 19). This pharmaceutical composition further comprises also -16), a surfactant (claims 20-22) and may be applied to the nasal mucosa (claim 23). Nagano et al. does not teach the combination of ciclesonide with that of an antihistamine.

Nishibe et al. teaches a pharmaceutical composition for application to mucosa, whereby the osmotic pressure of the composition and a hemostatic agent promote increased mucosal absorption and bioavailability of a medicament (see abstract). One embodiment of the Nishibe et al. pharmaceutical composition comprises an aqueous solution, one or more hemostatic agent, one or more water-insoluble or water-low

soluble substance, one or more medicament, and an osmotic pressure of less than 290 mOsm (¶16). Nishibe et al. further teaches agents used for treating allergies, including the following: *azelastine hydrochloride, terfenadine, astemizole, emedastine fumarate, epinastine hydrochloride,* as well as, steroids used in the treatment of rhinitis and asthma (see col. 3, ¶22, in its entirety). Further, Nishibe et al. teaches the essential components necessary to change the osmotic pressure of the pharmaceutical composition as well as the resulting effect on drug bioavailability (see col. 3, ¶ 23-¶30 and col. 3-8, Tables 1 to 8),

> "In particular, when osmotic pressure is as low as 5 mOsm (composition No. 29) or 7 mOsm (composition No. 33), residual ratio in the nasal cavity is very high at about 50%. The result indicates that a drug, that permeates into the blood after a single administration of the drug, stays at the mucosa without permeating into the blood when coadministered with a hemostatic agent, and thereby the usefulness of the present invention has been shown for the drugs of which efficacy depends on the amount of the drug and on the time of retention at the local mucosa which may lead to side effects. Furthermore, it has been shown that the amount remaining in the mucosa is greater for the pharmaceutical preparations having low osmotic pressure for which the amount permeated to the blood is greater, and therefore the usefulness of the present invention becomes even greater when the pharmaceutical preparation has a low osmotic pressure," (see col. 9, ¶55).

A preferred combination of water-soluble polymer and water-insoluble or water-low soluble substance for the Nishibe et al. pharmaceutical composition is a mixture of carboxymethyl cellulose sodium and crystalline cellulose (see ¶ 26, col. 3, lines 65-67 and spanning to lines 1-3).

Thus, the pharmaceutical composition found in Nishibe et al. for mucosa administration of medicaments comprises anti-allergy medicaments, of which the drug classes (antihistamines and steroids) are included and claimed (see col. 9, claim 29).

Both Nagano et al. and Nishibe et al. teach aqueous pharmaceutical compositions which are applied to mucosa using solutions possessing different osmotic pressures (mOsm) resulting in an improved bioavailability of medicaments. The pharmaceutical composition of Nagano et al. discloses that the steroid, ciclesonide, is absorbed by the mucosa and retained locally thus limiting its harmful systemic effects and instead, increasing its pharmacological effectiveness. Nishibe et al. teaches that aqueous solutions with low osmotic pressure are beneficial for agents that are applied to the mucosa, such as those agents used for the treatment of allergies. Included among the anti-allergy agents are antihistamine drugs, such as, azelastine hydrochloride, terfenadine, epinastine hydrochloride, emedastine fumarate, and astemizole as well as steroids (i.e., beclomethasone dipropionate, fluticasone propionate, flunisolide and mometasone) which are used in the treatment of rhinitis (allergic) and asthma (22nd ¶, in its entirety), however this list of steroids does not include ciclesonide. Because the aqueous solution composition containing ciclesonide, taught by Nagano et al., demonstrated (1) limited systemic effects, (2) improved bioavailability and (3) increased pharmacological effectiveness when the aqueous solution had a low osmotic pressure, it would have been *prima facie* obvious, to one of ordinary skill in the art, to substitute ciclesonide for one of the steroids taught by Nishibe et al. in order to formulate a combination drug for treatment of allergy symptoms and asthma with lower risk of systemic side effects, improved bioavailability and increased pharmacological effectiveness.

Applicants' claims 9 and 12 drawn to use of the water-insoluble polymer microcrystalline cellulose is an obvious variant of the crystalline cellulose described in the pharmaceutical composition of Nishibe et al. and thus deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan. Accordingly, this type of modification would have been well within the purview of the skilled artisan and no more than an effort to optimize results.

Conclusion

In conclusion, no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard A. Houghtling, Ph.D. whose telephone number is 571-272-9334. The examiner can normally be reached Monday to Thursday from 8:00 am - 5:00 pm. The examiner can also be reached on alternate Fridays (9 am – Noon).

The Group 1600 fax phone number where this application or proceeding is assigned is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center representative whose telephone number is (571)-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached on 571-272-0911.

Richard A. Houghtling, Ph.D.

JEFFREY STUCKER
SUPERVISORY PATENT EXAMINER